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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
06/18/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,338	WARNAAR ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-2, 4, 8-12, are 14-17* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1,2,4,8-10,12 and 14-17* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The Amendment filed March 13, 2007 in response to the Office Action of November 16, 2006 is acknowledged and has been entered. Claims 3, 5-7, and 13 are canceled, claims 1-2, 4, 8-12, are 14-17 pending, claim 11 is withdrawn from consideration as being drawn to a non-elected invention, and claims 1-2, 4, 8-10, 12, and 14-17 are under examination.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-2, 4, 8-10, 12, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bleumer et al., (January 2002, European Urology Supplements, Vol. 1, No. 1, pp. 112) in view of Pavone (2001, Cancer Immunol. Immunother. 50:82-86).

The claims, as drawn to the elected invention, are as follows:

a method for the treatment of renal cell cancer comprising co-administering an anti-tumor antibody and a cytokine to a subject in need thereof, wherein the cytokine is an interferon and is administered continuously or repeatedly in a low-dose form, wherein the low-dose cytokine comprises a dose which is pharmaceutically effective in the absence of NIC CTC toxicity grade 3 or higher (**claim 1**),

comprising a daily administration of a low-dose cytokine (**claim 4**),

wherein the cytokine is IFN-α (**claim 8**),

wherein the cytokine is IFN-α, wherein the dose of IFN-α is in the range of from 1-10 MIU three times a week (**claim 9**),

wherein the cytokine is administered in a constant dose during the treatment. (**claim 10**),

wherein the cytokine is administered subcutaneously (**claim 12**),

wherein the antitumor antibody is a chimeric or humanized G250 antibody or a fragment thereof (**claim 14**),

wherein the antitumor antibody is administered in intervals of from 5-20 days. (claim 15),

and

a method for the treatment of renal cell cancer comprising co-administering an anti-tumor antibody directed against the MN antigen and cytokine to a subject in need thereof, wherein the cytokine is an interferon and the method comprises: (a) a first treatment stage comprising administering a low-dose cytokine, and (b) a second treatment stage comprising co-administering an anti-tumor antibody and a low-dose cytokine, and wherein the low-dose cytokine comprises a dose which is pharmaceutically effective in the absence of NIC CTC toxicity grade 3 or higher (**claim 2**),

wherein the first treatment stage comprises 5-20 days (**claim 16**),

wherein the second treatment stage comprises 50-200 days (**claim 17**),

Bleumer et al. teaches a phase II clinical trial with monoclonal antibody WX-G250, a chimeric monoclonal antibody, in patients with advanced renal cell carcinoma, wherein the patients were pretreated (e.g. with IL-2 and interferon-alpha) and weekly dose of WX-G250 was given by iv infusion for 12 weeks. Bleumer et al. concluded that the weekly schedule of WX-G250 was safe, and very well tolerated for the 12 week treatment regimen.

Bleumer teaches as set forth above but does not teach the continuous or repeated administration of interferon-alpha in low dose form.

Pavone et al. teaches that there is no standard treatment for advanced renal cell carcinoma (RCC), but that recombinant interleukin-2 (rIL-2) and interferon-α (rIFN-a) have produced good results to inducing objective responses and especially prolonged survival, although the optimal dose and schedule of immunotherapy have yet to be determined (page 82). Pavone further teaches a study wherein patients having

advanced renal cell carcinoma were treated with a combination therapy of rIL-2, given by subcutaneous injection for 5 days per week ($1x10^6$ IU/m^2 every 12 h on days 1 and 2, followed by $1x10^6$ IU/m^2 on days 3-5), and rIFN-alpha given twice a week (1.8×10^6 IU/m2 on days 3 and 5) for four consecutive weeks, with the cycle being systemically repeated every 4 months) (page 83). Pavone et al. further teaches that the above described study indicated that long-term repeated cycles of low doses of rIL-2 and rIFN-a were found to induce a repeated and significant expansion of CD3-CD56+ NK cells, one of the most important lymphocyte subsets for the immune response to tumoral antigens, with the results supporting the long-term repetitive treatment of tumors susceptible to immunotherapy (page 86).

It is prima facie obvious to combine the two stage interferon-alpha/G250 antibody treatment taught by Bleumer with the continuous low dose interferon-alpha treatment taught by Pavone to arrive at a method wherein alpha-interferon is administered coincident with antibody treatment for the treatment of renal cell carcinoma. The idea of combining them flows logically from their having been individually taught in prior art (e.g. In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art). One of skill in the art would have been motivated to combine the therapies because of the known intractability of renal cell carcinoma to therapy. One of skill in the art would have a reasonable expectation of success in making the combination because of the demonstrated success of each of the therapeutic methods individually. Further, as set forth in MPEP 2144.05, in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art", a prima facie case of obviousness exists. In re Wertheim 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990)..

Further, given the conventional nature of dosage administration titration, it would have been prima facie obvious for one of skill in the art to have titrated the administration protocols for the combination of the anti-tumor antibody directed against the MN antigen and low dose cytokines in order to optimize the efficacy of the combined anti-renal cell carcinoma therapy to arrive at first treatment stage of 5-20 days and daily administration of the low-dose cytokine in order to optimize the efficacy of the combined anti-renal cell carcinoma therapy.

Although Pavone et al. does not specifically teach the absence of NIC CTC toxicity grade 3 or higher, given that dosage employed in Pavone is within the suggested range for the instantly claimed invention i.e. (1-10 MIU as recited in claim 9), it would be expected that the toxicity of the treatment was below the specified level. Thus, the claimed method appears to be the same as the prior art method. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the prior art does not possess the same method steps of the claimed process. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed methods of treating cancer are different than those taught by the prior art and to establish patentable differences. See In re Best 562 F.2d 1252, 195 USPQ430 (CCPA 1977) and Ex Parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

All other rejections from the Office action of November 16, 2006 are withdrawn.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8700.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Catherine M. Joyce
Examiner
Art Unit 1642

/Karen A. Canella, Ph.D./

Primary Examiner, Art Unit 1643